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REMARKS/ARGUMENTS

Claims 1-30 are pending in the application. Claims 1, 18 and 30 have been amended herein to recite that after deposition of the various solutions and before merging occurs, the device is permitted to reach thermal equilibrium. Support for these amendments is found throughout the specification, for example at paragraph [0045]. Therefore, no new matter is added by these amendments.

Rejection Under 35 USC §103

Claims 1-30 stand rejected under 35 USC §103(a) as unpatentable over Lehto et al., WO 99/54730 ("Lehto") in view of Verwaerde et al., US Published Application No. 2004/0038227 ("Verwaerde"). The examiner contends that Lehto teaches a method of performing biochemical analysis using small amounts of liquid sample that comprises the merging of two sample solutions comprising a drug candidate and a drug target on a substrate using electrostatic forces, including the use of parallel electrodes arranged on a substrate for facilitating the transport and manipulation of sample droplets during processing and analysis, and the use of temperature controlled environment. The examiner acknowledges the failure of Lehto to teach detecting and comparing the heats of reaction during the analysis, but looks to Verwaerde for the teaching of the benefits to use of a microcalorimeter. Applicants traverse.

The subject invention involves a method for high throughput screening assay sample preparation and analysis, using a device that measures enthalpy of reaction, comprising introducing a library compound solution to a first solvent solution such that the two mix upon contact, in place on the device, followed by introducing a target compound/second solvent solution onto the device; establishing thermal equilibrium of the device; merging the library compound/solvent solution with the target compound/solvent solution at a first location on the device; merging the library compound/solvent solution with a third solvent at a second location; detecting the heat of reaction from each merger reaction; and comparing the results. The amendments to

independent claims 1, 18 and 30 require that the device be allowed to establish a thermal equilibrium prior to merging of the solutions.

Lehto teaches using small sample sizes, drops of which are transported, as the examiner has pointed out in the rejection, along tracks on the device of Lehto. Lehto uses a changing electric field to transport the sample droplets through a series of steps (note the disclosure at pages 7–8 and 25-38 as cited by the examiner), where the sample and target are each transported to anew position on the device and are mixed with solvent and then with a marking ligand, such as a fluorescing compound, then rinsed, and then passed through a detector that quantifies fluorescence. See also Figure 1 of the reference. According to the reference, the sample must first be merged with a carrier and a label; each of these components is initially added at different positions on the device. The three drops are then transported and then merged and undergo incubation at another position on the device. At yet another position on the device the merged drop is washed to remove any unbound ligand so that the fluorescence data is not compromised. Finally, it is moved one last time to undergo detection of fluorescence from the label. In all, the reference requires that the sample move through no less than 4 positions on the device. The subject invention merges the drops of solution in the same position in which they are deposited, i.e., an electrostatic force is applied which causes the drops to expand and contact one another, or merge. In addition to this difference, claims 1, 18 and 30 require that the drops on the device be allowed to achieve or establish thermal equilibrium before any contact or merger takes place, so that only the enthalpy of the desired reaction, or binding reaction, is then measured. Lehto fails to even suggest establishing a thermal equilibrium on the device, and requires transport of drops through various device positions.

In addition to the foregoing, as the examiner points out, Lehto fails to teach using a nanocalorimeter. Instead, Lehto use fluorescence, which requires the added step of washing to remove unbound label. There would be no need for Lehto to use a nanocalorimeter in the method disclosed in that reference. In addition, Lehto makes no mention of use of a method wherein mixing and detection all occur in the

same location on the device. Lehto requires the use of electrodes and an appropriate field to move the sample droplets through the necessary positions on the device in order to get accurate results with regard to fluorescence.

Verwaerde also lacks any teaching or suggestion to allow the device to establish thermal equilibrium between any deposition and merging or mixing steps. Verwaerde does suggest using a microcalorimeter. Any combination of this teaching, however, falls short of disclosing the claimed invention, which comprises introducing a library compound solution to a first solvent solution such that the two mix upon contact, in place on the device, followed by introducing a target compound/second solvent solution onto the device; establishing thermal equilibrium of the device; merging the library compound/solvent solution with the target compound/solvent solution at a first location on the device; merging the library compound/solvent solution with a third solvent at a second location; detecting the heat of reaction from each merger reaction; and comparing the results. Between the cited references, there is no teaching to allowing the device to establish thermal equilibrium prior to initiating merging or mixing, which generates a heat of reaction that is then detected by a nanocalorimeter.
Given that the Lehto reference consistently teaches the use of fluorescing markers to detect reaction or binding, one skilled in the art would not be likely to consult Verwaerde for temperature dependent detection methods. However, even if one did combine the references, the combination fails for the reasons stated above. Further, neither reference teaches the use of a method that mixes target and solution and sample and solution in the same spot where detection will occur, eliminating the need for multiple processing steps occurring at different locations on a device, as is disclosed in Lehto.

Dependent claims 2-17, depending directly or ultimately from independent claim1, and dependent claims 19-29, depending directly or ultimately from independent claim 18, are considered to include all of the limitations of the independent claim from which they depend. As such, the arguments presented above are equally applicable to each of the dependent claims.

Conclusion

Given the foregoing, it is respectfully requested that the examiner reconsider the rejection of claims 1-30 under the combination of Lehto and Verwaerde, and withdraw the same. Should the examiner have any questions regarding this submission, a telephone call to the undersigned attorney would be welcome.

Respectfully submitted,

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